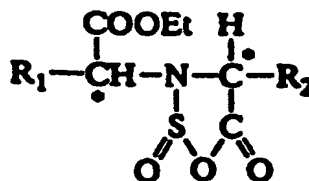




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(54) Title: N-SULFOXY ANHYDRIDES, A PROCESS FOR THE PREPARATION THEREOF AND ITS USE FOR THE PREPARATION OF BIOACTIVE SUBSTANCES HAVING ACE INHIBITORY ACTION (57) Abstract Novel N-sulfoxy anhydrides, a process for the preparation thereof and its use for the preparation of bioactive substances having ACE inhibitory action. Novel compounds of formula (III), wherein R ₁ represents PhCH ₂ -CH ₂ - or CH ₃ CH ₂ -CH ₂ - and R ₂ represents methyl or R ₃ -NH-(CH ₂) ₃ -CH ₂ -, wherein R ₃ has the meaning of amino protective group, are disclosed. They are used as intermediates in the synthesis of ACE inhibitors, especially of enalapril andtrandolapril.		



(III)

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N-sulfoxy anhydrides, a process for the preparation thereof and its use for the preparation of bioactive substances having ACE inhibitory action

Technical Field

The present invention is from the field of chemical synthesis and relates to novel N-sulfoxy anhydrides, to a process for the preparation thereof as well as to the use thereof for a simple and cheap preparation of bioactive substances having ACE inhibitory action.

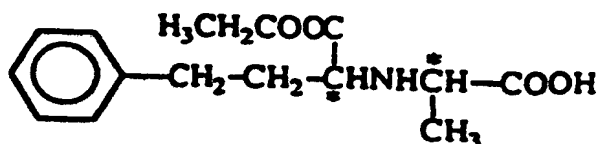
Technical Problem

There was a need for a simple and industrially suitable process for the synthesis of active derivative that would be appropriate as starting material for the synthesis of ACE inhibitors disclosed e.g. in Drugs of the future 1992, 17(7), 551-558. and others.

Prior Art

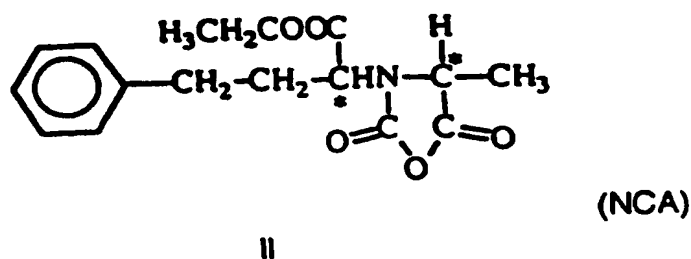
For the preparation of ACE inhibitors two types of processes are most frequently used. The first one is a reductive amination, which is difficult to be carried out on industrial scale and is disclosed in US 4,374,829.

The second type uses e.g. N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-N-carboxy-anhydride (NCA; see the formula (II) below) as reactant. In EP 0215335 A2 the reaction of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine of the formula (I)



I

with phosgene and polymers thereof is disclosed and there is obtained N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-N-carboxy-anhydride (NCA) of the formula (II)



which is reacted with salts and esters of L-proline to enalapril.

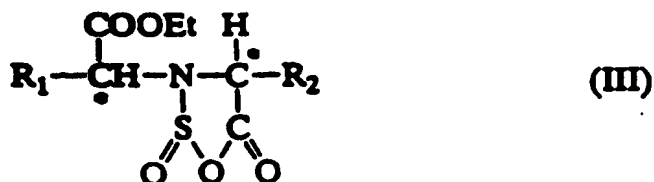
The preparation of active NCA is also described in EP 0114067, wherein a reaction of phosgene with amino acid (I) is disclosed. In EP 0061768 A1 the preparation of NCA (II) by a reaction of amino acid (I) and carbonyl diimidazole (CDI) is disclosed. The preparation of NCA is also disclosed in ES 2004804. The NCA (II) formed is then reacted with silylated L-proline (YU patent application 1355/88) and with non-silylated L-proline (SI patent 9200213) to enalapril and enalapril maleate, resp., which is an interesting ACE inhibitor.

In all disclosed cases of activation of amino acid (I) there are used toxic phosgene, phosgene polymers (diphosgene, triphosgene) or phosgene derivatives such as CDI, which may be prepared by only a few phosgene producers. The use of CDI for activating amino acid (I) is expensive and it is also necessary to regenerate the waste imidazole, which may be converted again into CDI only by a phosgene producer.

Also in the synthesis oftrandolapril disclosed in EP 0088341 and in US 4,490,386, for activating the compound (I) expensive carbonyl diimidazole CDI is used, which is converted into the corresponding NCA (II).

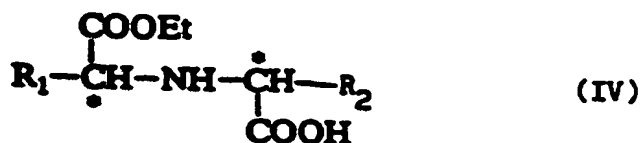
Technical Solution

The first object of the invention are novel N-sulfoxy anhydrides of the formula (III) (NSA)



wherein R_1 represents $\text{PhCH}_2\text{-CH}_2\text{-}$ or $\text{CH}_3\text{CH}_2\text{CH}_2\text{-}$ and R_2 represents methyl or $R_3\text{-NH-(CH}_2)_3\text{-CH}_2\text{-}$, R_3 being an amino protecting group, preferably $\text{CF}_3\text{CO-}$.

The second object of the invention is a process for the preparation of novel N-sulfoxy anhydrides of the formula (III), characterized in that a compound of the formula (IV)



wherein R_1 in R_2 have the above meanings, is reacted with an N-(chlorosulfinyl)-heterocyclic compound of the general formula (V)



V

wherein R_4 represents the rest of imidazole, of alkyl imidazole, of benzimidazole, of tetrazole and of similar other heterocyclic compounds.

Compounds of the general formulas (IV) and (V) are commercially available or may be prepared according to processes known from the literature.

The preparation of the compound of the general formula (V), wherein R_4 is an imidazole rest, i.e. chlorosulfinyl imidazole, is disclosed e.g. in *Synthetic Communications*, 10 (10), 733-742, 1980, Masaru Ogata and Hiroshi Matsumoto. In the reaction in dry methylene chloride between SOCl_2 and imidazole in a 1:4 ratio there are obtained N,N'-thionyl-diimidazole and imidazole hydrochloride, which is filtered off. An equimolar amount of thionylchloride is added to the filtrate with N,N'-thionyl-diimidazole and two molar equivalents of N-chlorosulfinyl imidazole of the formula (V) are obtained.

The preparation of the compound of the general formula (V), wherein R_1 is a benzimidazole rest, i.e. N-chlorosulfinyl benzimidazole, is disclosed in *Synthetic Communications*, 10 (7), 559-567, 1980, Masaru Ogata and Hiroshi Matsumato.

The reaction between the compound of the formula (IV) and the compound of the general formula (V) is carried out in dry organic solvents (humidity < 0.04%), preferably in chlorinated organic solvents such as methylene chloride, or non-chlorinated organic solvents such as ethyl acetate, dimethyl carbonate, diethyl carbonate, acetonitrile etc.

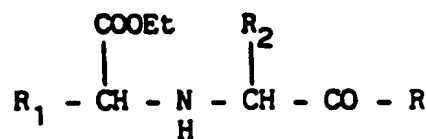
The reaction between the compound of the formula (IV) and the compound of the formula (V) is carried out at a temperature between -15°C and +25°C.

The formed hydrochloride of a heterocyclic compound, e.g. imidazole HCl, methylimidazole HCl, benzimidazole HCl, tetrazole HCl etc., is filtered off or sucked off. Organic bases may be regenerated and recycled.

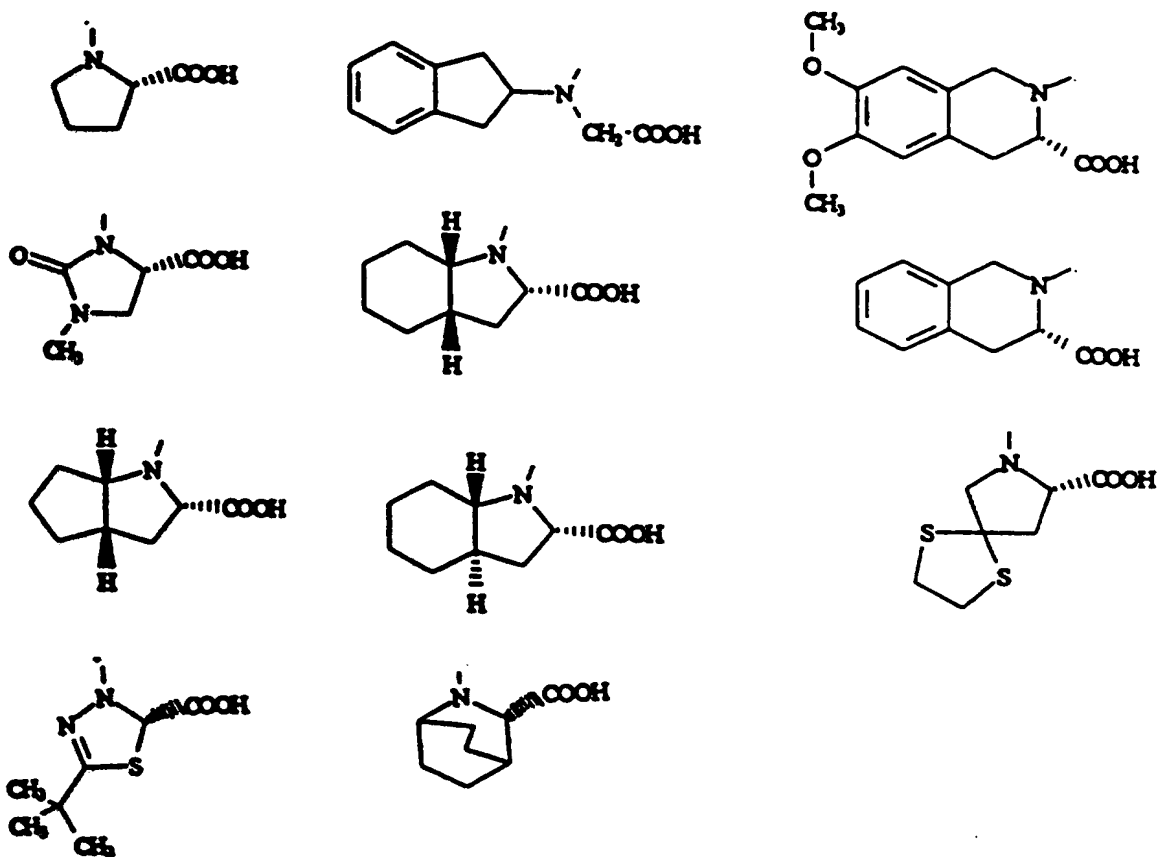
The pure novel compound of the formula (III) (NSA) remains in the organic solvent. The formation of the compound NSA is confirmed by

- a) quantitative isolation of a heterocyclic compound corresponding to the rest R_1 in the form of hydrochloride, in two reaction steps;
- b) iodometric titration of the amount of SO_2 formed after the hydrolysis of NSA;
- c) IR spectroscopy of the solution of a sample having characteristic absorption bands at 1820 cm^{-1} , 1750 cm^{-1} in 1030 cm^{-1} ;
- d) NMR spectra which do not contain signals for protons of the heterocyclic compound (V) used;
- e) a further reaction of NSA with silylated amino acids under release of SO_2 .

The third object of the invention is a process for the preparation of corresponding ACE inhibitors, wherein NSA (III) is reacted with corresponding derivatives of amino acids defined below. More particularly, the object of the invention is a process for the preparation of ACE inhibitors of the formula

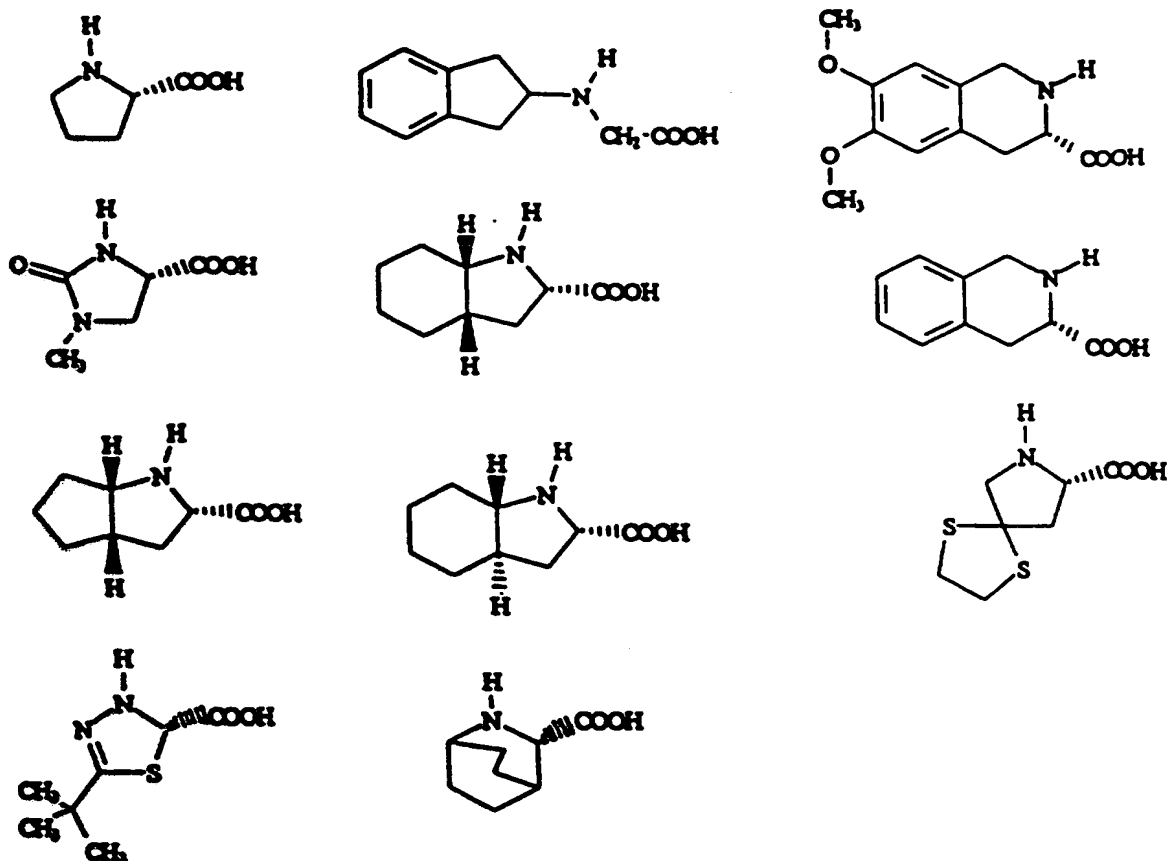


in racemate form as well as in the form of pure stereoisomers, and pharmaceutically acceptable salts thereof such as hydrochloride, maleinate, sulfate, wherein R_1 and R_2 are defined as above and R has the following meanings



characterized in that the compound NSA of the formula III is reacted with

- a) mono- or disilylated amino acids or with mixtures of mono- and disilylated amino acids selected from the group consisting of



at a pH from 2 to 6, preferably 2 to 3, or

b) with inorganic or organic salts of amino acids defined as under a) at a pH over 7, or

c) with a free amino acid defined as under a), preferably with L-proline.

and then the obtained compounds are converted in a conventional way into pharmaceutically acceptable salts thereof such as hydrochloride, maleinate, sulfate.

As inorganic salts e.g. potassium or sodium salts are used.

As organic salts preferably salts of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). DBN (1,5-diazabicyclo[4.3.0]non-5-ene). TEA (triethylamine). tetramethylguanidine. imidazole. methylimidazole etc. are used.

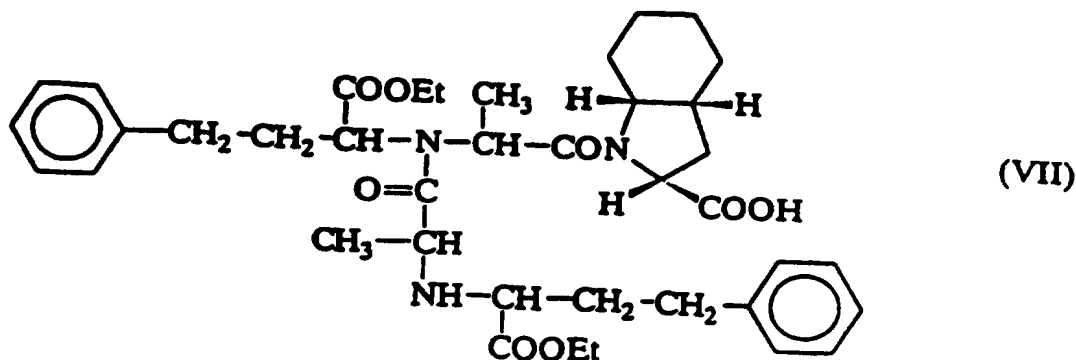
In the case of amino acid N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine (I) after activation with N-chlorosulfinyl imidazole NSA N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-N-sulfoxyanhydride is obtained, which is reacted with

L-proline, silylated L-proline or with an organic or inorganic salt of L-proline to enalapril.

If the same NSA (III) is reacted with a mixture, a silylated mixture or with an organic or inorganic salt of the mixture of 2S,3aS,7aS- and 2R,3aR,7aR-octahydro-1H-indole-2-carboxylic acid, there is obtained a racemic mixture of SSS and RRR ACE inhibitor having the chemical name 2S,3aS,7aS- or 2R,3aR,7aR-1-{2S-[(1R-ethoxycarbonyl-3-phenylpropyl)amino]-1-oxopropyl}octa-hydro-1H-indole-2-carboxylic acid. If as octahydro-1H-indole-2-carboxylic acid a pure isomer is used such as 2S,3aS,7aS or 2S,3aR,7aS, SSS or SRS trandolapril is obtained (see J. Med. Chem. 1987. 30, 992-998).

For the preparation of enalapril the novel compound of the formula (III) (R_1 means $\text{PhCH}_2\text{-CH}_2\text{-}$, R_2 means methyl), which remains in the organic solvent such as methylene chloride after sucking off the hydrochloride of heterocyclic compound such as imidazole hydrochloride and is very reactive, is reacted with silylated L-proline (process variant a) or with inorganic or organic salt of L-proline as defined above (process variant b), to N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline (known as enalapril) with a high yield. During the reaction a gaseous SO_2 is released, which also proves the existence of the novel compound NSA of formula (III). The reaction between NSA and silylated L-proline is carried out in the temperature range from -20°C to $+25^\circ\text{C}$. This process is shown in Scheme 1.

In the process variant b) besides the desired ACE inhibitors also novel derivatives are formed, which in case of the preparation of trandolapril have the following formula VII



It may be identified with spectroscopic methods. In the mass spectrum the following signals m/z are present: 692 (M^+ , 18%), 431 (100%), 234 (78%), 170 (13%), 124 (29%), 91 (35%).

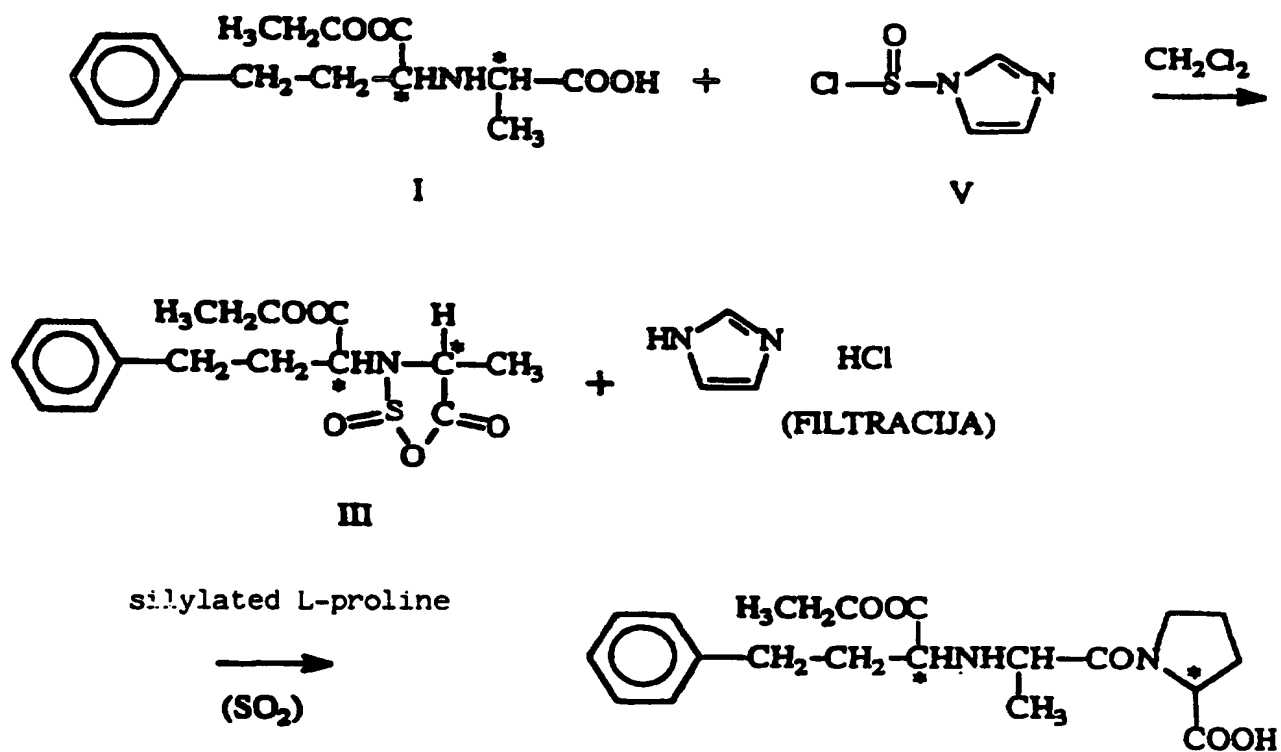
In the NMR spectrum of the compound VII the ratio between phenyl protons and the proton in position 2 in octahydroindole moiety is 10:1 and thereby the suggested structure of the compound of the formula (VII) is confirmed.

The use of the compound of the formula (III) as a starting substance makes possible an economical, effective and simple industrial process for the preparation of enalapril,trandolapril and other ACE inhibitors, especially when the process variant a) is used.

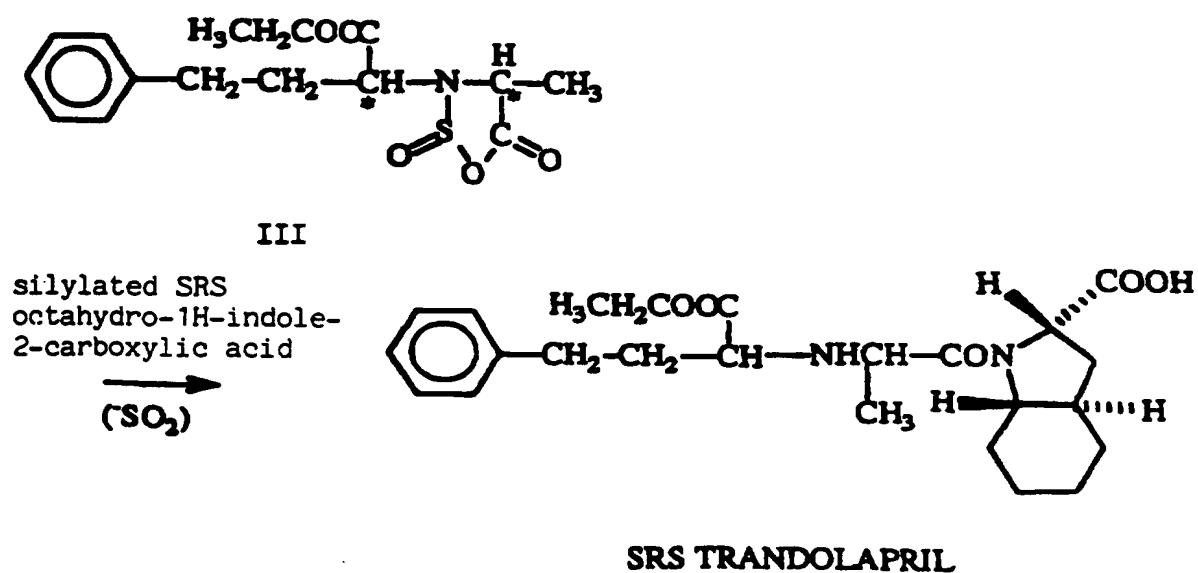
The use of NSA is very convenient since the condensation reaction proceeds well already at lower temperatures in the range of from -15°C to $+25^{\circ}\text{C}$. Imidazole and other ambident compounds useful in the synthesis of NSA may be isolated quantitatively and recycled. The process is ecologically pure since a major part of reactants may be regenerated and recycled.

Synthesised ACE inhibitors are recrystallized from acetonitrile or are purified by reprecipitation in ethyl acetate thus achieving high yields at purification (about 94%).

SCHEME 1



SCHEME 2

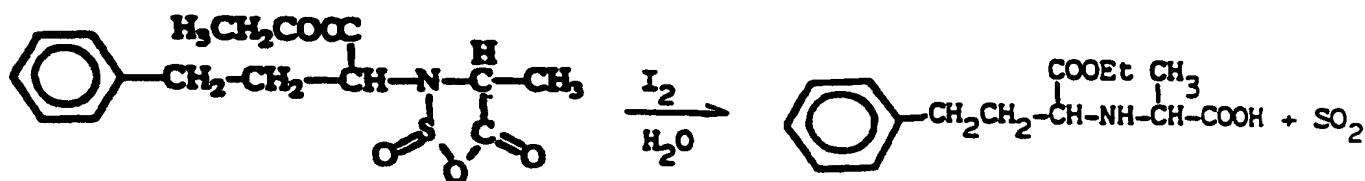


The invention is illustrated but in no way limited by the following Examples.

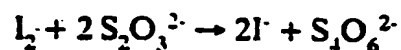
Example 1

Synthesis of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-N-sulfoxy anhydride (NSA, wherein R₁ means PhCH₂-CH₂- and R₂ means methyl)

SOCl₂ (0.18 ml; 0.0025 mole) was added to anhydrous methylene chloride (7 ml; water content according to Karl Fischer < 0.04%) and the mixture was cooled to -10°C and then imidazole (0.68 g; 0.01 mole) was added. During stirring for 60 minutes the temperature gradually increased to 15°C. The precipitate of imidazole hydrochloride was filtered off, washed with dry CH₂Cl₂ (5 ml) and a dry salt of imidazole hydrochloride (0.58 g) was obtained. The mother liquor was again cooled to -10°C and thionylchloride (0.18 ml; 0.0025 mole) was added. The solution was stirred for 60 minutes at a temperature between -10°C and +15°C. Then N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine (1.25 g; 0.0045 mole) and CH₂Cl₂ (16 ml) was added. After stirring for 65 minutes (the temperature increased from -15°C to +25°C), the precipitate was filtered off, washed with methylene chloride (5 ml) and a dry salt of imidazole hydrochloride (0.51 g) was obtained. After both filtrations imidazole hydrochloride could be regenerated and recycled. The mother liquor contained the novel compound N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-N-sulfoxy- anhydride or NSA, which was analyzed. NSA is oily liquid, unstable in humidity and air, and has a molecular weight 325 determined by iodometric titration on the basis of the following Scheme:

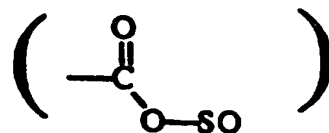


Excessive I₂ was determined by titration with thiosulfate:

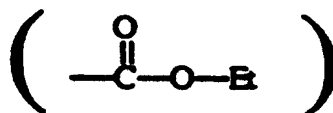


IR absorption cm^{-1}

1820 cm^{-1}



1750 cm^{-1}



1030 cm^{-1}



NSA thus prepared may be used as starting material for the synthesis of ACE inhibitors.

Example 2

Synthesis of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline maleinate

a) Preparation of silylated L-proline

Trimethylchlorosilane (5.7 ml; 0.045 mole) was added to a mixture of L-proline (2.47 g; 0.0215 mole), anhydrous methylene chloride (90 ml) and triethylamine (2.5 ml; 0.018 mole) and the mixture was stirred for 2 hours.

b) Thionylchloride (0.73 ml; 0.01 mole) was added to dry methylene chloride mixture (25 ml; $\text{H}_2\text{O} < 0.04\%$) and the mixture was cooled to -5°C . Then imidazole (2.72 g; 0.04 mole) was added. The mixture was stirred for 65 minutes at a temperature

between -5°C and room temperature 20°C . Then the separated imidazole hydrochloride was filtered off and washed with methylene chloride (5 ml) (the yield of dry imidazole hydrochloride 2.09 g). Thionylchloride (0.73 ml; 0.01 mole) was added to the mother liquor and the mixture was stirred for 60 minutes between -5°C and $+20^{\circ}\text{C}$. The reaction mixture was again cooled to -15°C and N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine (5 g; 0.0179 mole) in methylene chloride (65 ml) was added. The mixture was stirred for 65 minutes and during that time the temperature increased to 20 - 25°C .

Silylated L-proline was added to the reaction mixture containing only NSA. Acylation was controlled by IR spectroscopy - it was found that -C=O- vibration at 1820 cm^{-1} disappeared. The reaction was completed in a few hours depending upon reaction temperature. Then the slightly yellowish solution was evaporated on rotavapor and the solvent was removed and water (36 ml), NaCl (12 g) and ethyl acetate (18 ml) were added to the residue. The pH 2.66 was changed to pH 4.22 with 33% NaOH. The organic phase was separated and the aqueous phase was extracted twice with ethyl acetate (10 ml). The combined ethyl acetate was dried with anhydrous sodium sulfate, sucked off and washed with ethyl acetate (2 x 10 ml) and then methyl acetate (14 ml) was poured thereto. Maleic acid (2.14 g; 0.01844 mole) was added. The mixture was stirred for 20 minutes at room temperature and then for 20 minutes at -25°C . The precipitate formed was filtered off, washed with ethyl acetate and there was obtained enalapril maleate (6.2 g) (yield 88%), m.p. 144 - 146°C (in the literature 143 - 144.5°C). $[\alpha]_{20}^{\text{D}}$ 1% MeOH -44.16 (in the literature -42.2).

Example 3

Synthesis of SSS trandolapril

Anhydrous methylene chloride (7 ml) and SOCl_2 (0.18 ml; 0.0025 mole) were blended. The solution was cooled to -5°C and imidazole (0.68 g; 0.01 mole) was added (white suspension). The system was stirred for 1 hour and the temperature was allowed to increase from -5°C to room temperature. Then it was filtered off and solid was washed with CH_2Cl_2 (5 ml). The liquid was cooled to -5°C and additional SOCl_2 (0.18 ml) was added while stirring the system for 1 hour and allowing the temperature to increase from -5°C to room temperature. Then the system was cooled to -15°C and N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine (1.25 g; 0.0045 mole) and anhydrous CH_2Cl_2 (16 ml) were added. The system was stirred for 65 minutes

and the temperature was allowed to increase from -15°C to room temperature. Then it was filtered and the solid was washed with anhydrous CH_2Cl_2 (5 ml). An opalescent solution A (the preparation thereof is disclosed below) of silylated (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid was added to the filtrate and an opalescent yellow solution was obtained. This solution was stirred for 1 to 6 hours at room temperature (21°C). Then the solution of H_2O (10 ml) and NaCl (3 g) was added and 35% HCl was added to achieve pH 0.8. It was decanted and the organic phase was washed with water (5 ml). A solution of H_2O (10 ml) and NaCl (3 g) was added to the organic phase and 33% NaOH was added to achieve pH 4.33. Then it was decanted and the aqueous phase was washed with CH_2Cl_2 (5 ml). The organic phase was dried with anhydrous Na_2SO_4 , filtered and evaporated on rotavapor. After the evaporation of CH_2Cl_2 , methyl-tert.-butylether (about 20 ml) was added and it was again evaporated on rotavapor. 2S,3aS,7aS-1{2S-[(1R-ethoxycarbonyl-3-phenylpropyl)-amino]-1-oxopropyl}octahydro-1-H-indole-2-carboxylic acid (trandolapril base: 1.94 g) was obtained in a 100% yield, m.p. 60°C .

SSS trandolapril

IR: 1755, 1660, 1450, 1220 cm^{-1}

NMR: 7.14-7.32 (m, 5H); 4.46 (t, 1H); 3.95-4.22 (m, 6H); 2.25-2.4 (m, 3H); 2.05 (t, 1H); 1.4-1.85 (m, 5H); 1.31 (d, 3H); 1.23 (t, 3H); 0.9-1.35 (6H)

Mass spectrum: m/z 430 (M^+ , 2%); 429 ($\text{M}^+ - 1$, 14%); 368 (10); 357 (5); 339 (7); 308 (32); 262 (34); 234 (45); 206 (22); 160 (21); 147 (82); 117 (25); 91 (59); 73 (100); 57 (47).

Elemental analysis for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_5$:

	%H	%C	%N
calc.:	7.96	66.95	6.51
found:	8.13	66.55	6.31

Preparation of the solution A

(2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid (0.90 g; 0.0053 mole) was blended with anhydrous CH_2Cl_2 (25 ml), triethylamine (0.73 ml; 0.0053 mole) and

(CH₃)₃SiCl (0.67 ml; 0.0053 mole). The system was stirred for 1.5 to 2 hours at room temperature (21°C).

Example 4

Synthesis of SRS trandolapril

It was proceeded in the same way as in Example 3 with the difference that instead of SSS octahydro-1H-indole-2-carboxylic acid, the 2S,3aR,7aS isomer was used. SRS trandolapril 2S,3aR,7aS-1{2S-[(1R-ethoxycarbonyl-3-phenylpropyl)amino]-1-oxo-propyl}octahydro-1-H-indole-2-carboxylic acid (1.72 g). m.p. 140-143°C. was obtained.

Spectroscopic data:

IR: 1735; 1670; 1450; 1415; 1280 cm⁻¹

mass spectrum (FAB) m/z: 431 (M⁺ + 1, 52%); 307 (41); 289 (22); 234 (23); 154 (100); 137 (89); 120 (18); 107 (27); 89 (25); 77 (21)

Example 5

Synthesis of trandolapril sulfate

Trandolapril (0.5 g; 0.00116 mole) obtained in Example 3 and methyl-tert.-butyl ether (10 ml) were blended and a yellow solution was obtained. To this solution during 1 hour a sulfuric acid solution (0.5 ml; 0.00036 mole) (this solution was obtained in such a way that 1 ml of 96% sulfuric acid was diluted to 25 ml with methyl-tert.-butyl ether) was added at room temperature (22°C) and under good stirring. In 20 minutes another 0.3 ml (0.000216 mole) of the above sulfuric acid solution were added at -15°C to -20°C. The system was filtered at -20°C and the solid was washed with methyl-tert.-butyl ether (5 ml) at -20°C. A beige solid (0.41 g), which was trandolapril sulfate, was obtained with the yield 74.5%. m.p. 86 to 90°C.

*Example 6***Synthesis of trandolapril hydrochloride**

Trandolapril (0.5 g; 0.00116 mole) obtained in Example 3 and methyl-tert.-butyl ether (10 ml) were blended and a yellow solution was obtained. This solution was cooled at -15°C to -20°C and HCl gas was bubbled through it. The title product began to precipitate. Since the suspension was very thick, another 3 ml of methyl-tert.-butyl ether was added and HCl gas was bubbled through it (HCl gas was bubbled 5 to 10 minutes in total). The system was stirred at -15°C to -20°C for another 10 minutes and then filtered at this temperature. The solid was washed with methyl-tert.-butyl-ether (5 ml) at -20°C. A beige solid (0.43 g), which was trandolapril hydrochloride, was obtained with the yield 80%, m.p. 105 to 110°C.

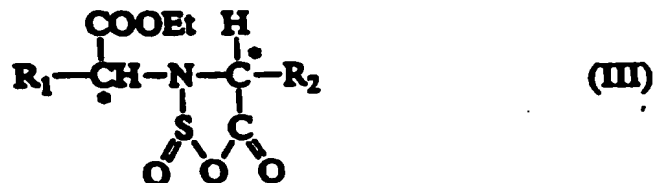
*Example 7***Synthesis of trandolapril (process variant b)**

A racemic mixture (0.9 g; 0.0053 mole) of 2S,3aS,7aS and 2R,3aR,7aR octahydro-1H-indole-2-carboxylic acid, anhydrous methylene chloride (22 ml) and tetramethylguanidine (TMG; 1.56 ml; 0.0124 mole) were blended. The mixture was stirred for 2 hours at 20°C.

To the mother liquor obtained in Example 1 and cooled to -5°C, some 4-N,N-dimethyl aminopyridine was added as a catalyst and the above solution was added drop by drop for 15 minutes at -5°C to 0°C. Then the system was stirred at -5°C to 0°C for 25 minutes and afterwards a solution of H₂O (10 ml) and NaCl (3 g) was added. 1 N HCl was added to achieve pH 4.21 and it was decanted. The aqueous phase was washed with methylene chloride (5 ml) and finally the organic phase was dried with anhydrous sodium sulfate, filtered and evaporated on rotavapor. A yellow solid paste was obtained. Methyl-tert.-butyl ether (15 ml) was added and it was again evaporated on rotavapor. A mixture (2 g) of trandolapril and of the compound of the formula VII was obtained.

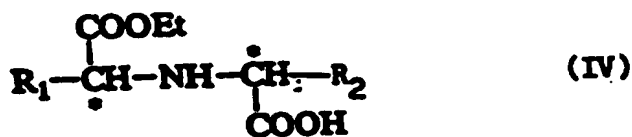
CLAIMS

1. N-sulfoxy anhydrides of the formula (III) (NSA)



wherein R_1 represents $\text{PhCH}_2\text{-CH}_2\text{-}$ or $\text{CH}_3\text{CH}_2\text{CH}_2\text{-}$ and R_2 represents methyl or $\text{R}_3\text{-NH-(CH}_2\text{)}_3\text{-CH}_2\text{-}$, R_3 being an amino protecting group, preferably $\text{CF}_3\text{CO-}$.

2. Process for preparing N-sulfoxy anhydrides of the formula (III) according to claim 1, characterized in that a compound of the formula (IV)



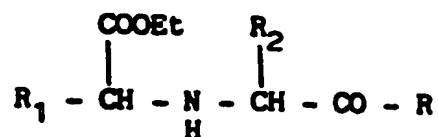
wherein R_1 in R_2 have the above meanings,
is reacted with a N-(chlorosulfinyl)-heterocyclic compound of the general formula (V)



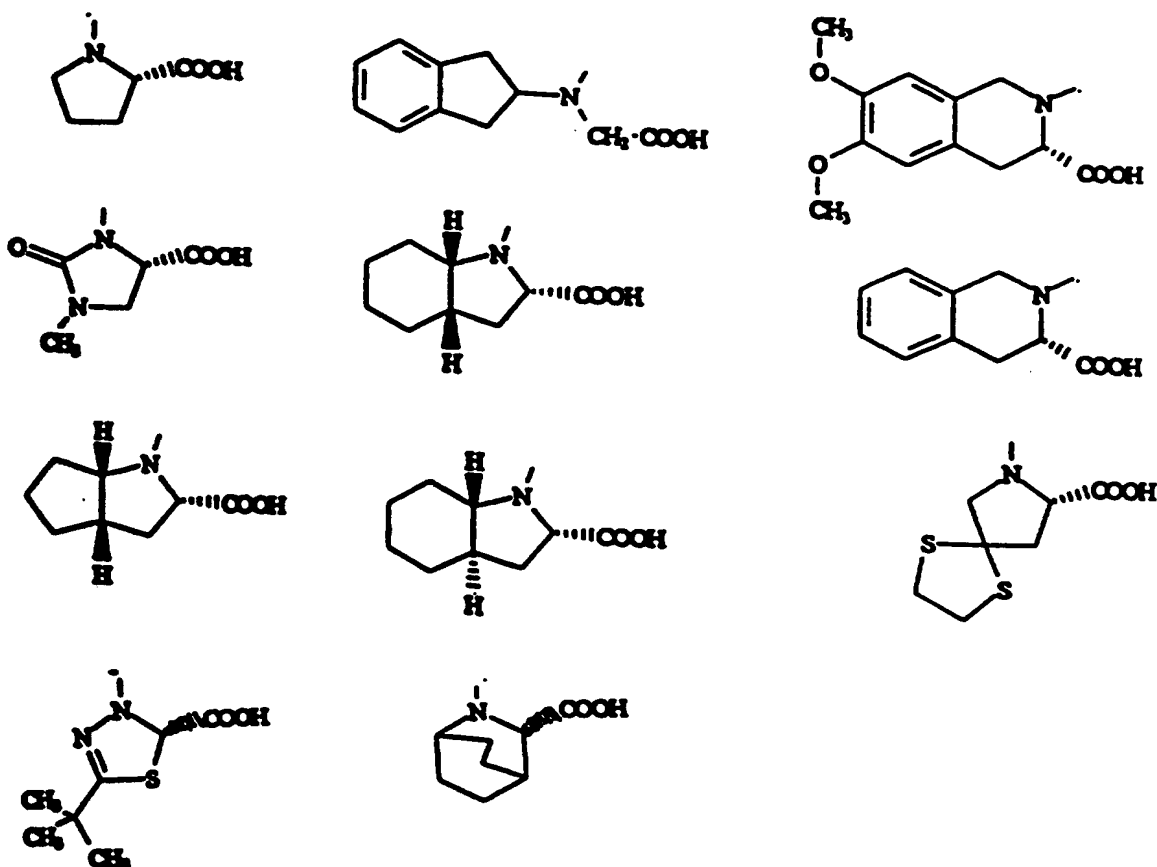
V

wherein R_4 represents the rest of imidazole, of alkyl imidazole, of benzimidazole, of tetrazole and of similar other heterocyclic compounds, in dry organic solvents.

3. Process for preparing ACE inhibitors of the formula

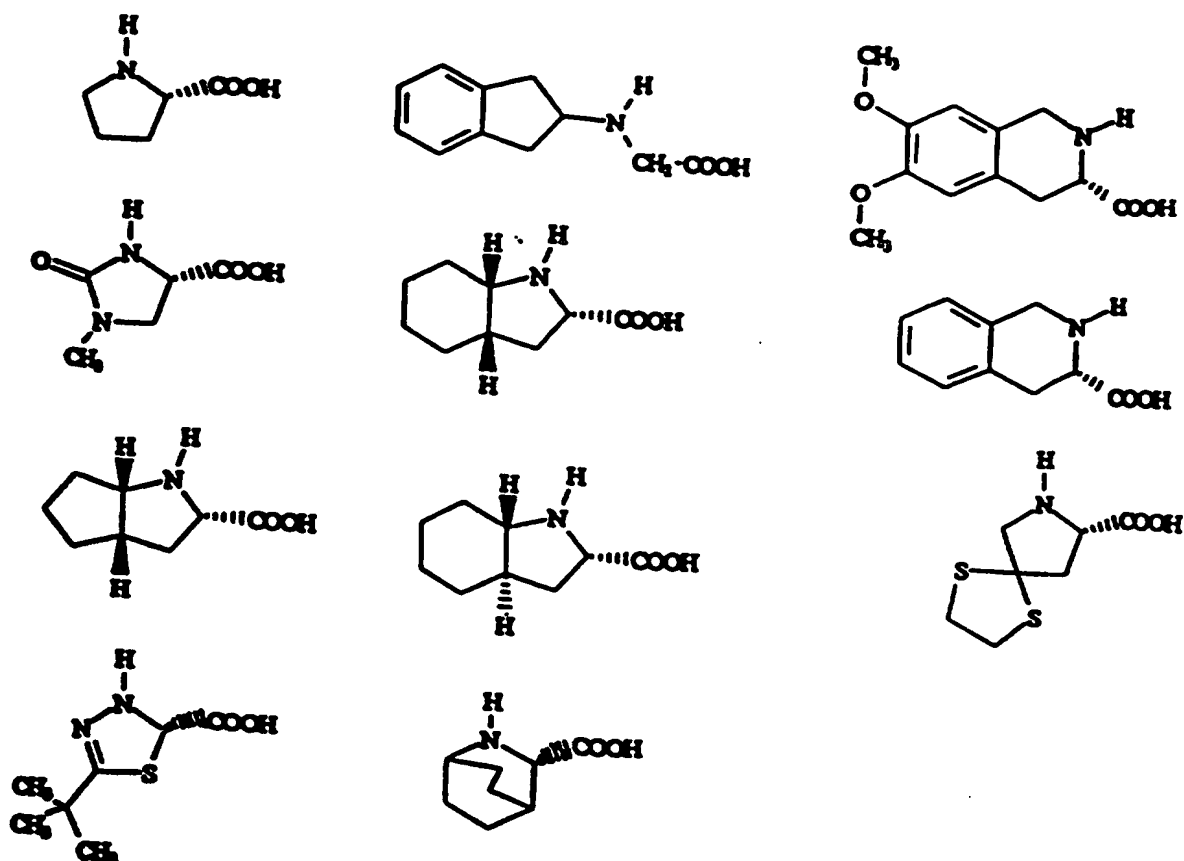


in the racemate form as well as in the form of pure stereoisomers, and pharmaceutically acceptable salts thereof such as hydrochloride, maleinate, sulfate, wherein R_1 and R_2 are defined as in Claim 1 and R has the following meanings



characterized in that the compound NSA of the formula III is reacted with

a) mono- or disilylated amino acids or with mixtures of mono- and disilylated amino acids selected from the group consisting of



at a pH from 2 to 6, preferably 2 to 3, or

b) with inorganic or organic salts of amino acids defined as under a) at a pH over 7.
or

c) with a free amino acid defined as under a), preferably with L-proline,

and then the obtained compounds are converted in a conventional way into pharmaceutically acceptable salts thereof such as hydrochloride, maleinate, sulfate.

4. Process according to claim 3, characterized in that enalapril andtrandolapril are prepared.

5. Process according to claim 3 or 4, characterized in that the synthesized ACE inhibitor is purified by recrystallization from acetonitrile or by reprecipitation in ethyl acetate.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/SI 96/00009

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D291/04 A61K31/41 C07D207/16 C07D209/42 A61K31/40
C07K5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 114, no. 9, 4 March 1991 Columbus, Ohio, US; abstract no. 81985x, LAVAYSSIERE ET AL: "Oxazoliones and dioxolones containing germanium (IV), germanium (II), phosphorus (III), sulfur." page 755; column 1; XP002008602 see abstract & PHOSPHORUS, SULFUR SILICON RELAT. ELEM., vol. 53, no. 1-4, 1990, pages 411-422, ---	1
A	EP,A,0 215 335 (KANEKAFUCHI KAKAKU KOGYO K.K.) 25 March 1987 cited in the application see page 4 - page 6 ---	1-5
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 July 1996

Date of mailing of the international search report

7.08.96

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INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/SI 96/00009

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 088 341 (WARNER-LAMBERT) 14 September 1983 cited in the application see claim 2 ---	1-5
A	EP,A,0 058 567 (WARNER-LAMBERT) 25 August 1982 see claim 1 -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No.

PCT/SI 96/00009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-215335	25-03-87	JP-C- 1833955	29-03-94
		JP-A- 62048696	03-03-87
		CA-A- 1329445	10-05-94
		DE-A- 3687103	17-12-92
		US-A- 4716235	29-12-87

EP-A-88341	14-09-83	US-A- 4350704	21-09-82
		AU-B- 543861	09-05-85
		CA-A- 1205476	03-06-86
		EP-A- 0037231	07-10-81
		EP-A- 0088342	14-09-83
		SU-A- 1246893	23-07-86
		SU-A- 1241988	30-06-86
US-A- 4425355	10-01-84		

EP-A-58567	25-08-82	AT-T- 8619	15-08-84
		EP-A- 0093805	16-11-83
		JP-A- 57158758	30-09-82
		US-A- 4503043	05-03-85
